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10/552,806	10/11/2005	Bernhard Gleich	DE 030116	5535
24737 7590 04/29/2011 PHILIPS INTELLECTUAL PROPERTY & STANDARDS P.O. BOX 3001 BRIARCLIFF MANOR, NY 10510			EXAMINER DEJONG, ERIC S	
			ART UNIT	PAPER NUMBER
			1631	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/552,806	Applicant(s) GLEICH, BERNHARD	
	Examiner ERIC S. DEJONG	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-17,19 and 41-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-17,19 and 41-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED OFFICE ACTION

Applicant's response filed 02/22/2011 is acknowledged,

Claim 4, 18, and 20-40 are cancelled. Claim 43 is newly presented. Claims 1-3, 5-17, 19, and 41-43 are pending and currently under examination.

Claim Rejections - 35 USC § 101

The rejection of claims 1-3, 5-17, 19, 41, and 42 under 35 U.S.C. 101 because the claimed invention lacks patentable utility is withdrawn in view of applicants amendments to the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-17, 19, and 41-43 recites the limitation "providing an indication of the determined at least one local substance concentration, temperature, pressure, viscosity and pH" in lines 26 and 27 of claim 1. There is insufficient antecedent basis for this limitation in the claim because there is no recitation of an active step of determining determined at least one local substance concentration, temperature, pressure, viscosity and pH. Rather, the instant claim has only been amended to recite the intended use (see lines 25 and 26 of claim 1) rather than the recitation of any positive active steps

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that results in the determination of " at least one local substance concentration, temperature, pressure, viscosity and pH".

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-17,19, and 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Collin et al. (Nucleic Acids Research (2000) in light of Evens (Biomolecular NMR Spectroscopy, Oxford Press, 1995) and Piotto et al. (Journal of Biomolecular NMR, 1992). This is newly applied to claim 43, which is necessitated by applicants amendments tot he instant claims.

The recited process comprises the steps of introducing into an examination area magnetic particles in a first state or a second state, wherein at least some of the magnetic particles that are to be examined are agglomerated and/or coupled to one another in the first state and deagglomerated and/or decoupled in the second state.

Collin et al. teaches the application of NMR experiments applied to samples of isotopically labeled DNA and RNA at 1mM concentrations recorded on a Bruker DRX-600 spectrometer and a Bruker DRX-800 spectrometer equipped with triple resonance,

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three-axis gradient probes. See Collin et al. page 3386, col. 2, line 35 through page 3387, col. 1., line 5.

Evans et al. is relied upon for support that the natural abundance of ^1H nucleic and isotopically enriched ^{15}N in the 1 mM concentration samples of isotopically labeled DNA and RNA, as taught by Collin et al., are magnetic particles. Specifically ^1H and ^{15}N nuclei are have a nuclear magnetic "spin" of $\frac{1}{2}$ and can exist in one of two quantum states, denoted as "up" and "down", with respect to large external magnetic field. See Evans et al., section 1.1 Basic Theory of NMR, pages 5-9 and Table 1.2.

The recited process further comprises generating a magnetic field having a field strength with a gradient profile, such that there is a produced in the examination area two part areas including a first part-area having low magnetic field and a second part area having a higher magnetic field strength. The recited process further comprises changing spatial positions of the two part areas or changing the magnetic field strength in the first part area to cause the change in the spatial distribution of magnetic particles so that magnetization of the particles is locally changed.

Collin et al. teaches the use of three-axis gradient probes and the application of NMR experiments involving the use of transverse gradients. See Collin et al., page 3386, col. 2, line 35 through page 3387, col. 1., line 32.

Piotto et al. is further relied upon for support that the WATERGATE pulse program procedure as applied and taught in Collin et al. comprises the application of magnetic field gradient pulse applied across the entirety of a sample under investigation. See Piotto et al., Abstract, page 662 in it's entirety, and Figure 1. The

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application of a field-gradient pulse introducing a magnetic field across the sample varies as a function of sample position, and therefore meets the recited limitation of a first and second area of differing magnetic field intensity.

The recited process further comprises detecting signals that depend on the magnetization in the examination area that is influenced by the changing act. The recited process further comprises evaluating signals so as to obtain information about the change in the spatial distribution of the magnetic particles and about physical, chemical, and/or biological state variables that include at least one substance concentration, temperature, pressure, viscosity, and pH, to which the change is correlated.

Collin et al. teaches the use of a 2D ^1H - ^{15}N HSQC experiment that involves detecting the magnetization properties of a concentrated nucleic acid sample in the form of a Free Induction Decay (FID) (see also Evans et al., page 11 and Figure 1.12). See Collin et al., page 3387, col. 1, lines 13-32. Collin et al. further teaches the evaluation of the collected data. See Collin et al., page 3387, col. 1, lines 20 and 21. Figure 1 is further relied upon to demonstrate that the information determined from the described NMR experiments involves and is directly correlated to sample concentration and pH dependencies.

Dependent claim 2 further recites the detecting act includes detecting change of the magnetic particles from the first state to the second state including deagglomeration and/or decoupling of coupled individual magnetic particles and/or detecting increased distance between magnetic particles.

Evans et al. is relied upon for support that the ^1H - ^{15}N HSQC NMR experiment of Collin et al. is selective for determining those ^1H and ^{15}N that are coupled to one another through covalent bonds that exist in a given molecule and is selective against those ^1H and ^{15}N that are not coupled and, therefore, do not share a covalent bond. See Evans et al., Sect. 2.1.6: Heteronuclear correlation spectroscopy, pages 66 through 71.

Dependent claim 3 further recites the detecting includes detecting passage of the magnetic particles between the first state and second state, the passage being due to at least one of heat, radiation, acid, base, electrical or magnetic fields, ultrasounds, and/or and enzyme.

Evans et al. is relied upon for support that the passage of magnetization between particles in a first and second state, as taught by Collin et al., is inherently an electromagnetic phenomenon. See Evans et al., Sect. 2.1.6: Heteronuclear correlation spectroscopy, pages 66 through 71.

Dependent claim 5 recites that the act of spatially delimiting the agglomerated magnetic particles in a medium which can be physically, chemically, and/or biologically modified, dissolved, and/or modified.

Figure 1 of Collin et al. is relied for demonstrating that the aqueous compositions under analysis can be modified to contain different concentrations of both DNA and RNA samples as well as to contain different buffering conditions and agents.

Dependent claim 9 recites that the act of saturating the magnetic particles by act of application of an external magnetic field having a strength of about 100mT or less.

Piotto et al., Figure 2 is relied upon for support that the WATERGATE NMR procedure used by Collin et al. involves the application of 17.5 kHz non-selective and 165 Hz selective RF, which correlates to a field strength of the corresponding electromagnetic pulse to less than 100mTesla.

Dependent claims 10 and 12 recite the magnetic particles are monodomain or multidomain and further comprising the act of reversing magnetization of the multidomain or monodomain particles by Neel's rotation and Brown's rotation. Dependent claim 11 and 12 recites wherein the magnetic particles are hard-magnetic or soft-magnetic particles.

Table 1.2 of Evans et al is relied upon for support that ^1H and ^{15}N of Collin et al. are inherently dipolar spin $\frac{1}{2}$ particles whose quantized spin state can be influence by Neel's and Brown's rotation.

Dependent claim 13 recites binding magnetic particles to functional binding units including a functional group, a DNA sequence, and RNA sequence, and an aptamer, and introducing at least one compound which has complementary binding units and an aptamer sequence that interact in a binding manner with at least one functional binding unit of the magnetic particles.

Collin et al. presents the results of the above described NMR procedures and analysis on an RNA-DNA aptamer complex consisting of a 18 nt RNA hairpin and a 20 nt DNA aptamer. See Collin et al., Abstract.

Dependent claim 41 recites the act of changing magnetic fields includes changes the magnetic field strength temporally in a first frequency band and the detecting act

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includes detecting the signal in a second frequency band and the second frequency band including harmonics of signals in the first frequency band. Dependent claim 42 recites the act of generating the magnetic field further includes the act of first and second magnetic fields which change at different rates and with different amplitudes, wherein the first magnetic field changes slowly in time and the second magnetic field changes rapidly in time terms and with lower amplitude relative to the first magnetic field.

Evans et al. is relied upon for support that the use of a low power, saturating RF frequency pulse applied on the solvent resonance frequency during data collection, as taught in the method of Collin et al., inherently suppresses unwanted solvent signature. See Evans et al., Sect. 2.1.8 Solvent Suppression, pages 75-76.

Response to Arguments

Applicant's arguments filed 02/22/2001 have been fully considered but they are not persuasive.

Applicants first requested clarification of the claim rejection as being based upon 35 USC 103(a) or 35 USC 10(b).

In response to applicant's request for clarification, the instant claim is based on 35 USC 102(b) where the anticipatory reference relied upon is that of Collin et al. The text book reference of Evens et al. and Piooto et al. are relied upon in the instant rejection to provide support for inherent features of the NMR experimental processes set forth in Collin et al. As such, the instant claim is made on the basis of anticipation as

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set forth under 35 USC 102(b) and not an obviousness type rejection set forth under 35 USC 103(a).

In regards to the rejection of claims under 35 USC 102(b) applicants argue that Collin et al. does not teach the use of magnetic particles in two states, namely agglomerated and deagglomerated.

In response, applicants argument is not persuasive because the claimed "magnetic particles" are not differentiated over that set forth in the prior art. Collins et al. discloses the use of spin $\frac{1}{2}$ as the observed magnetic particle, which exists in two distinct states of "up" and "down". Further, as evidenced by Evans et al., the disclosed NMR investigation set forth by Collins et al. requires the use of coupled (agglomerated) and decoupled (deagglomerated) magnetic states of said observed magnetic particles.

Applicants further argue that the prior art does not teach introducing into the examination area magnetic particles that are agglomerated and deagglomerated and wherein the magnetic field has a low field strength in a first area and a high magnetic field in a second area.

In response, applicant's argument is not persuasive because the prior art does teach the use of magnetic particles that exist in two distinct pin states that participate in coupled and decoupled interactions as set forth above. Further the prior art expressly teaches the use of magnetic field gradient applied to the sample in an NMR spectrometer under investigation. This explicitly reads on applying a magnetic field that

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has a low field strength in a first area and a high magnetic field in a second area, where in said area encompasses the introduction of magnetic particles under investigation to an "examination area".

Applicant's further argue the prior art does not teach the determination of local variables such as local substance concentration, temperature, pressure, viscosity, and/or pH.

In response, it is reiterated from the instant rejection that Collin et al. teaches the use of a 2D ^1H - ^{15}N HSQC experiment that involves detecting the magnetization properties of a concentrated nucleic acid sample in the form of a Free Induction Decay (FID) (see also Evans et al., page 11 and Figure 1.12). See Collin et al., page 3387, col. 1, lines 13-32. Collin et al. further teaches the evaluation of the collected data. See Collin et al., page 3387, col. 1, lines 20 and 21. Figure 1 is further relied upon to demonstrate that the information determined from the described NMR experiments involves and is directly correlated to sample concentration and pH dependencies. Therefore, applicant's argument is not persuasive because the art expressly teaches the derivation of local concentration and pH dependency of a NMR sample under investigation.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ERIC S DEJONG/

Primary Examiner, Art Unit 1631